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# Bimetallic Redox Synergy in Oxidative Palladium Catalysis

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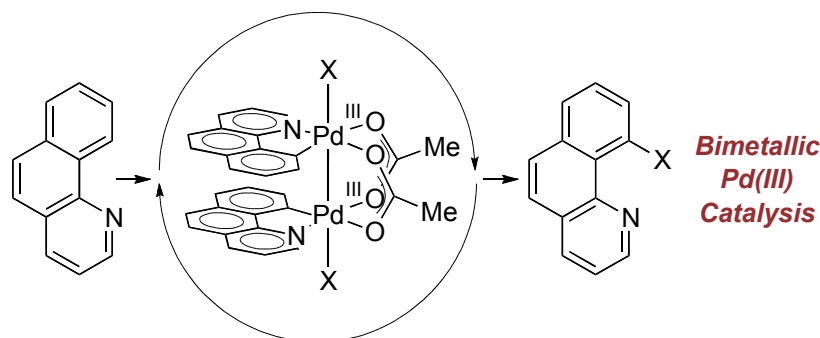
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**Conspectus.**



Polynuclear transition metal complexes, which are embedded in the active sites of many metalloenzymes, are responsible for effecting a diverse array of oxidation reactions in nature. The range of chemical transformations remains unparalleled in the laboratory. With few noteworthy exceptions, chemists have primarily focused on mononuclear transition metal complexes in developing homogeneous catalysis. Our group is interested in the development of carbon–heteroatom bond-forming reactions, with a particular focus on identifying reactions that can be applied to the synthesis of complex molecules. In this context, we have hypothesized that bimetallic redox chemistry, in which two metals participate synergistically, may lower the activation barriers to redox transformations relevant to catalysis. In this Account, we discuss redox chemistry of binuclear Pd complexes and examine the role of binuclear intermediates in Pd-catalyzed oxidation reactions.

Stoichiometric organometallic studies of the oxidation of binuclear Pd<sup>II</sup> complexes to binuclear Pd<sup>III</sup> complexes and subsequent C–X reductive elimination from the resulting binuclear Pd<sup>III</sup> complexes have confirmed the viability of C–X bond-forming reactions mediated by binuclear Pd<sup>III</sup> complexes.

Metal–metal bond formation, which proceeds concurrently with oxidation of binuclear Pd<sup>II</sup> complexes, can lower the activation barrier for oxidation. We also discuss experimental and theoretical work that suggests that C–X reductive elimination is also facilitated by redox cooperation of both metals during reductive elimination. The effect of ligand modification on the structure and reactivity of binuclear Pd<sup>III</sup> complexes will be presented in light of the impact that ligand structure can exert on the structure and reactivity of binuclear Pd<sup>III</sup> complexes.

Historically, oxidation reactions similar to those discussed here have been proposed to proceed via mononuclear Pd<sup>IV</sup> intermediates, and the hypothesis of mononuclear Pd<sup>II/IV</sup> catalysis has guided the successful development of many reactions. Herein we discuss differences between monometallic Pd<sup>IV</sup> and bimetallic Pd<sup>III</sup> redox catalysis. We address whether appreciation of the relevance of bimetallic Pd<sup>III</sup> redox catalysis is of academic interest exclusively, serving to provide a more nuanced description of catalysis, or if the new insight regarding bimetallic Pd<sup>III</sup> chemistry can be a platform to enable future reaction development. To this end, we describe an example in which the hypothesis of bimetallic redox chemistry guided reaction development, leading to the discovery of reactivity distinct from monometallic catalysts.

## Introduction

Polynuclear transition metal complexes, embedded in the active sites of metalloenzymes, are catalysts for redox chemistry in Nature.<sup>1</sup> Polynuclear iron, copper, nickel, cobalt, and manganese sites comprise many of Nature's redox catalysts, and collectively accomplish a remarkably diverse set of redox reactions, still unparalleled in the laboratory.<sup>1a</sup> For example, a binuclear iron site in soluble methane monooxygenase effects the selective hydroxylation of methane to methanol, coupled to the four-electron reduction of dioxygen.<sup>1b</sup> Nature has evolved highly efficient redox machinery based on polynuclear active sites. With some notable exceptions, chemists have primarily focused on mononuclear catalysts for development of homogeneous catalysis.

Our research has been motivated by the hypothesis that metal–metal (M–M) redox synergy can provide lower energy barrier pathways for carbon–heteroatom bond-forming reactions than are accessible with mononuclear catalysts. Cooperative redox chemistry between two metals may enable the construction of a variety of C–X bonds under conditions that are compatible with functionalized, complex small molecules. We have selected Pd(OAc)<sub>2</sub>-catalyzed C–H functionalization chemistry as the venue to study bimetallic redox synergy for two reasons. First, acetate-bridged binuclear Pd complexes contain two Pd centers held in proximity by bridging acetate ligands.<sup>2</sup> We reasoned that the

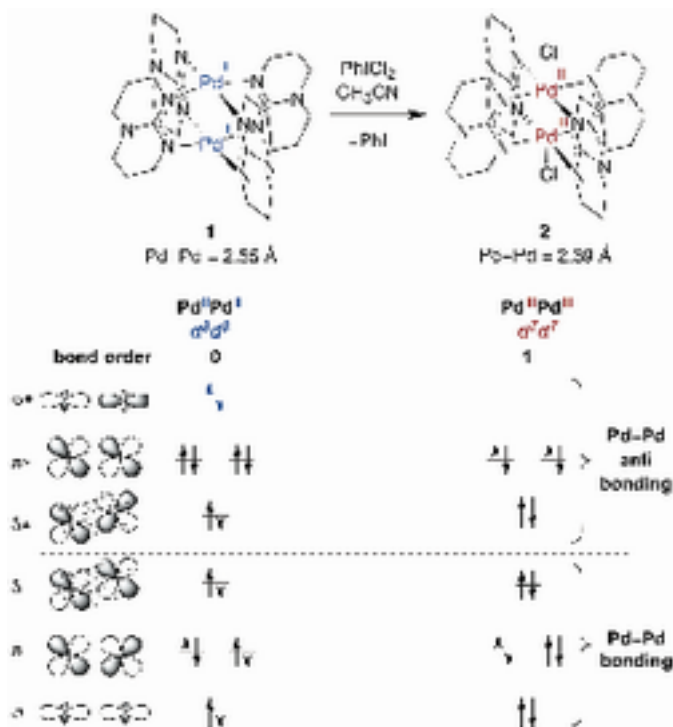
proximity of the metal centers might facilitate cooperative redox chemistry. Second, Pd-catalyzed C–H functionalization reactions have been developed in which a variety of C–X bonds are formed, many of which have been difficult to form with other transition metal catalysts.<sup>3</sup>

In this Account, we will first address aspects of fundamental organometallic chemistry of binuclear Pd<sup>III</sup> complexes. We will discuss the role of the binuclear palladium unit in both the oxidation to, and reductive elimination from, binuclear Pd<sup>III</sup> complexes. Emphasis will be given to the differences in reactivity that are expected for binuclear Pd<sup>III</sup> complexes as compared to mononuclear Pd<sup>IV</sup> complexes. Subsequently, the relevance of binuclear Pd<sup>III</sup> complexes to catalysis will be discussed. Reactions for which there is detailed experimental and theoretical evidence in support of binuclear intermediates in catalysis, as well as reactions in which the potential role of binuclear intermediates is more speculative, will be presented.

### Binuclear Pd<sup>III</sup> Chemistry

Ligand-bridged binuclear Pd<sup>II</sup> complexes are common.<sup>4</sup> Based on a simplified molecular orbital diagram for binuclear paddlewheel complexes containing  $d^8$  metals, such as **1**, there is no formal M–M bond (Scheme 1).<sup>4b,5</sup> Second-order, symmetry-allowed mixing of the Pd  $4d_{z^2}$ ,  $5p_z$ , and  $5s$  orbitals can result in weak Pd–Pd bonding; Pd–Pd bond orders of approximately 0.1 have been predicted computationally.<sup>6</sup> Binuclear Pd complexes with Pd in oxidation states higher than +II are rare.<sup>4a,7</sup> Binuclear Pd<sup>II</sup> complexes were first oxidized electrochemically in 1987,<sup>8</sup> but it was not until 1998, when Cotton reported the isolation of *tetra*-bridged binuclear Pd<sup>III</sup> complex **2**, that a high-valent binuclear Pd complex was isolated and characterized.<sup>9</sup> Contraction of the M–M distance, observed for the oxidation of binuclear Pd<sup>II</sup> complex **1** to binuclear Pd<sup>III</sup> complex **2**, is consistent with Pd–Pd bond formation upon oxidation (Scheme 1).<sup>9a,10</sup>

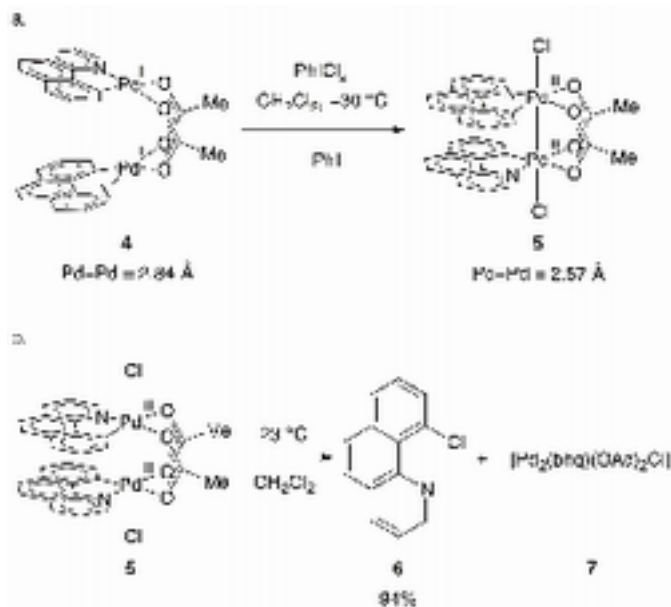
**Scheme 1.** Oxidation of binuclear Pd<sup>II</sup> complex **1** to binuclear Pd<sup>III</sup> complex **2** results in Pd–Pd bond formation and is accompanied by contraction of the Pd–Pd distance.



In 2009, we reported that acetate-bridged binuclear Pd<sup>II</sup> complex **4**, the product of cyclopalladation<sup>11</sup> of benzo[*h*]quinoline (**3**) with Pd(OAc)<sub>2</sub>, is oxidized to thermally sensitive binuclear Pd<sup>III</sup> complex **5** with PhICl<sub>2</sub> (Scheme 2a).<sup>12</sup> Complex **5** is diamagnetic, consistent with a spin-paired M–M bond between two *d*<sup>7</sup> Pd<sup>III</sup> centers. Oxidation of **4** to **5** results in contraction of the Pd–Pd distance by 0.27 Å, also consistent with M–M bond formation upon oxidation. Warming complex **5** results in formation of **6** and Pd<sup>II</sup> byproducts (**7**) (Scheme 2b), confirming the viability of C–X reductive elimination from binuclear Pd<sup>III</sup> complexes. The precise structure of the Pd<sup>II</sup> complex immediately following reductive elimination is unknown. The mixture of Pd<sup>II</sup> complexes (**7**), with empirical formula [Pd<sub>2</sub>(bhq)(OAc)<sub>2</sub>Cl], may result from rapid ligand rearrangement of the putative coordinatively unsaturated binuclear Pd<sup>II</sup> complex immediately following C–Cl reductive elimination. Both experimental and computational investigations support a reductive elimination mechanism in which the binuclear core of **5** remains intact during C–Cl reductive elimination.<sup>12</sup> Observation of thermally promoted C–Cl bond-forming reductive elimination from **5** represents the first example of an established carbon–heteroatom reductive elimination from a binuclear transition metal complex, and the first reported organometallic

transformation from Pd<sup>III</sup>.

**Scheme 2.** a. Oxidation of binuclear Pd<sup>II</sup> complex **4**, formed by cyclometallation of **3** with Pd(OAc)<sub>2</sub>, with PhICl<sub>2</sub> results in the formation of thermally sensitive binuclear Pd<sup>III</sup> complex **5**. b. Thermolysis of **5** results in **6** and **7**, the products of C–Cl reductive elimination. The C–Cl reductive elimination reaction proceeds without cleavage of the binuclear core. (bhq = benzo[*h*]quinoliny).



## Metallicity of Redox Transformations

Observation of oxidation to, and reductive elimination from binuclear Pd<sup>III</sup> complexes provides information regarding the number of metal centers involved in such redox transformations, but it does not address the role of the metal centers in the redox steps. For example, while two Fe centers are present in binuclear model systems of methane monooxygenase,<sup>1b</sup> there is currently debate about whether one or both of the metals participate in the redox chemistry associated with substrate oxidation.<sup>13</sup> Two metal centers may be present in the transition state of a redox transformation (binuclear), but if only one metal center participates in redox chemistry, the reaction is monometallic, not bimetallic. To address fundamental mechanism questions related to M–M redox synergy, discussion

of the number of metal centers present during a redox transformation needs to be distinguished from discussion of the role of each metal during redox chemistry. We have found the following two-tiered nomenclature scheme<sup>12b</sup> to be useful in describing redox transformations:

- Nuclearity – descriptor of structure; the number of metal centers in a redox transformation.
- Metallicity – descriptor of mechanism; the number of metal centers that participate in redox chemistry during a redox transformation.

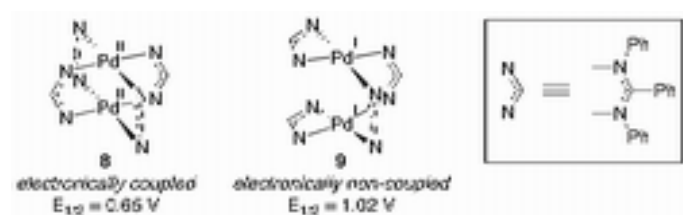
The mechanisms of oxidation from **4** to **5** and reductive elimination from binuclear Pd<sup>III</sup> complex **5** are not the microscopic reverse of one another. Oxidation results in formation of new metal–ligand bonds between each of the Pd centers and the respective apical ligands. Reductive elimination results in formation of a new C–X bond between two ligands on the same metal center. Because oxidation and reductive elimination do not proceed through the same transition state, the factors that favor oxidation do not necessarily disfavor reductive elimination. Below, we will discuss structural aspects of binuclear Pd complexes which provide access to low-activation-barrier redox pathways, and we will find that both oxidation and reductive elimination steps are facilitated by M–M redox synergy in the transition state.

### **Bimetallic Oxidative Addition**

To evaluate whether the oxidation of binuclear Pd<sup>II</sup> complex **4** to binuclear Pd<sup>III</sup> complex **5** is bimetallic, we must evaluate whether oxidation occurs prior to or concurrent with Pd–Pd bond formation. Comparison of crystallographically determined Pd–Pd bond lengths in binuclear Pd<sup>II</sup> and binuclear Pd<sup>III</sup> complexes cannot be used as evidence for the simultaneity of oxidation and Pd–Pd bond formation because Pd–Pd distances in binuclear Pd complexes are ground state properties and provide no information regarding the role of the individual Pd centers during oxidation. Electrochemical properties of complexes **8** and **9**, which differ only in the connectivity of the ligands to the metals, suggest that Pd–Pd bond formation can stabilize high-valent binuclear Pd complexes.<sup>14</sup> In complex **8**, all four ligands are bridging the two Pd centers, while in complex **9**, two ligands are bridging and two ligands are chelating the two Pd centers. The different metal–ligand connectivity imposes different

Pd–Pd separations: the Pd–Pd distance in **8** and **9** are 2.576(1) and 2.900(1) Å, respectively. The one-electron oxidation potential for the oxidation of **8** to **8**<sup>+</sup> (the Pd<sup>II</sup>Pd<sup>II</sup> to Pd<sup>II</sup>Pd<sup>III</sup> redox couple) is 370 mV lower than the potential necessary for one-electron oxidation of **9**, which is consistent with M–M bond formation stabilizing the products of oxidation.

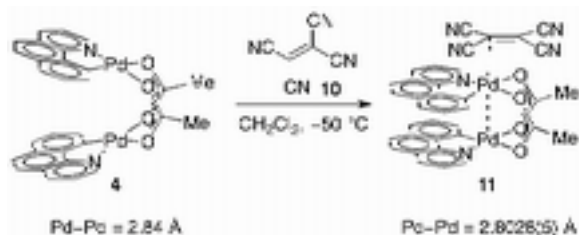
**Scheme 3.** The HOMO of **8**, in which the Pd centers are electronically coupled, is 370 mV higher in energy than the HOMO of **9**, in which the palladium centers are not electronically coupled. Potentials are relative to SCE in CH<sub>2</sub>Cl<sub>2</sub>.



To probe the simultaneity of oxidation and Pd–Pd bond formation, charge transfer complex **11**, the adduct of binuclear Pd<sup>II</sup> complex **4** and electron acceptor tetracyanoethylene (**10**), was prepared. Complex **11** is a transition state mimic for the oxidation of binuclear Pd<sup>II</sup> to binuclear Pd<sup>III</sup> and illustrates M–M bond contraction during oxidation (Scheme 4).<sup>15</sup> Tetracyanoethylene can accept electron density from the binuclear core of **4** without effecting formal oxidation to Pd<sup>III</sup> and as such allows observation of a snapshot of a structure between binuclear Pd<sup>II</sup> and binuclear Pd<sup>III</sup>. The Pd–Pd distance in **11** is 2.8028(5) Å, a contraction of 0.04 Å from complex **4**, and consistent with an increase in the Pd–Pd bond order in the reaction of **4** with **10**.

**Scheme 4.** Pd–Pd contraction in charge transfer complex **11** as compared to binuclear Pd<sup>II</sup> complex **4** indicates that Pd–Pd bond formation proceeds simultaneously with oxidation.

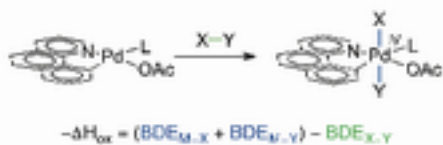




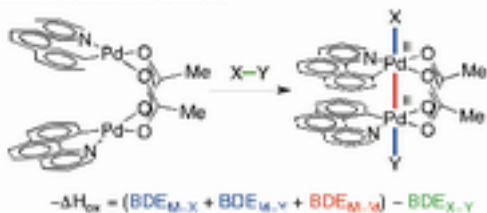
Together, the electrochemical properties of **8** and **9** and the observed metal–metal contraction in **11** suggest that Pd–Pd bond formation stabilizes binuclear Pd(III) complexes and that Pd–Pd bond formation can facilitate oxidation. A simple analysis of the relative energies ( $\Delta H_{ox}$ ) of mono- versus bimetallic oxidation reveals the potential for lower barrier bimetallic oxidation processes when the geometrical requirements for Pd–Pd bond formation are met (Scheme 5). During monometallic oxidation, the oxidant X–Y bond is cleaved and new Pd–X and Pd–Y bonds are formed. In a bimetallic oxidation, the same X–Y bond is cleaved, but in addition to the new Pd–X and Pd–Y bonds, a Pd–Pd bond is formed. While the analysis in Scheme 5 is based on thermodynamic parameters (bond dissociation energies (BDEs)), the activation barrier for bimetallic oxidation could be lower than that for monometallic oxidation because the nascent M–M bond in the oxidation transition state could lower the transition state energy relative to a case in which M–M bonding is not possible (i.e. monometallic oxidation).

**Scheme 5.** Bimetallic oxidation could be facilitated as compared to monometallic oxidation because partial Pd–Pd bond formation in the oxidation transition state could lower the activation barrier for oxidation as compared to monometallic oxidation, in which Pd–Pd bond formation is not proceeding in the oxidation transition state. The BDEs of Pd–X and Pd–Y bonds are not necessarily the same in mononuclear Pd<sup>IV</sup> and binuclear Pd<sup>III</sup> complexes.

#### Monometallic Oxidative Addition



#### Bimetallic Oxidative Addition



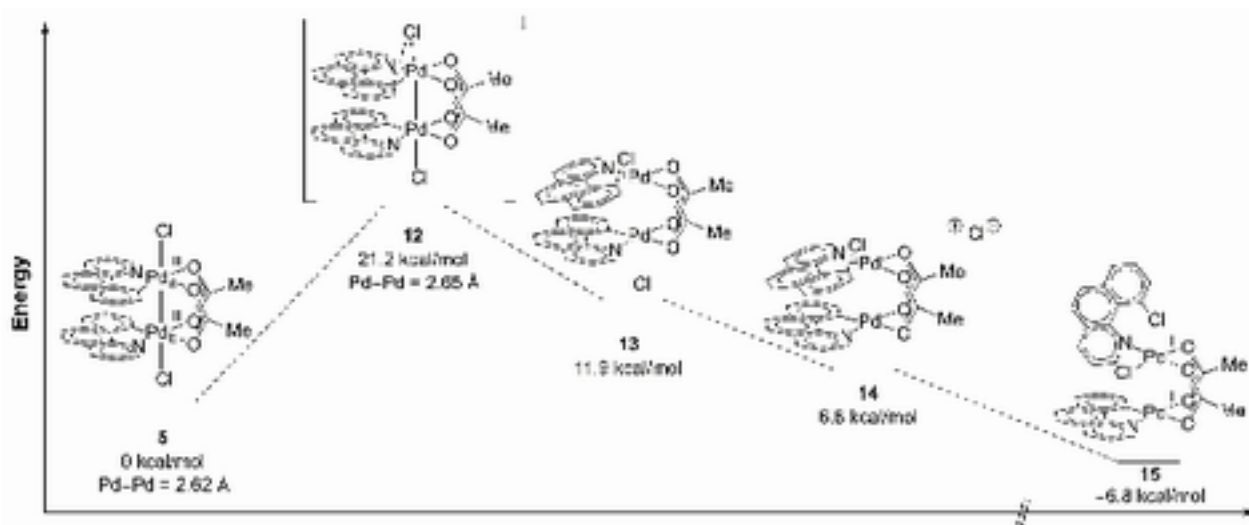
### Bimetallic Reductive Elimination

Carbon–heteroatom reductive elimination from binuclear  $\text{Pd}^{\text{III}}$  complexes could proceed via a number of mechanisms. Experimental results are consistent with C–Cl reductive elimination from **5** proceeding from a complex in which the binuclear core has not fragmented; for an example in which Pd–Pd fragmentation may be relevant, see below ‘Relevance of  $\text{Pd}^{\text{II}}\text{Pd}^{\text{IV}}$  Intermediates.’ While experimental results can address the nuclearity of reductive elimination, no experimental observables have been identified which are correlated with the metallicity of the reductive elimination process. We have used computational chemistry to investigate the role of each metal during reductive elimination and have found that monometallic pathways, proceeding through either valence-localized  $\text{Pd}^{\text{II}}\text{Pd}^{\text{IV}}$  or  $\text{Pd}^{\text{I}}\text{Pd}^{\text{III}}$  intermediates, are not relevant to C–Cl bond formation.<sup>12b</sup> Valence-localized structure, such as a mixed-valence  $\text{Pd}^{\text{I}}\text{Pd}^{\text{III}}$  intermediate could arise from one-centered redox chemistry in which electronic communication through the Pd–Pd bond is slow on the time scale of reductive elimination. Both metals are involved in redox chemistry during reductive elimination.

Computational evaluation of the mechanism of C–Cl reductive elimination from complex **5** revealed that the transition state for reductive elimination is early with respect to the metal–metal bond cleavage reaction coordinate; the calculated Pd–Pd distance for binuclear complex **5** is 2.62 Å, and the Pd–Pd distance in transition state **12** is 2.65 Å, only 0.03 Å longer than in complex **5** (Scheme 6).<sup>12b</sup> Because

the Pd–Pd bond is not significantly cleaved in the transition state, the chloride ligand involved in reductive elimination is still subject to the strong trans influence of the Pd–Pd bond. M–M bonds typically exhibit strong trans influences,<sup>16</sup> and during the reductive elimination from **5**, the strong trans influence of the Pd–Pd bond might facilitate reductive elimination.<sup>17</sup>

**Scheme 6.** Computational investigation of the mechanism of C–Cl reductive elimination from **5** indicates that the Pd–Pd bond is not cleaved in the transition state. Pd–Pd distances are calculated; DFT calculations were carried out at the M06/LACV3P++\*(2f) level.



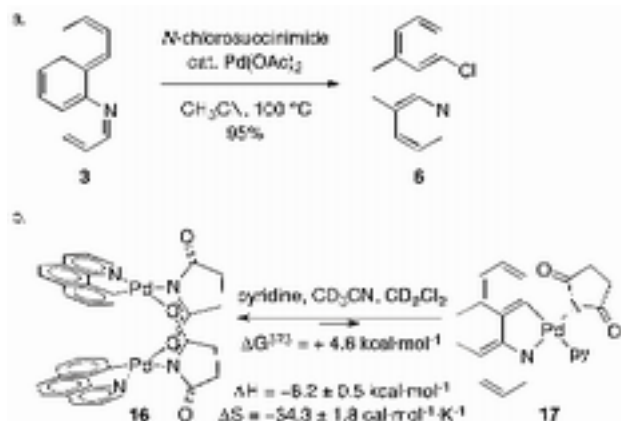
The contribution of each Pd center to the redox chemistry of reductive elimination was computationally evaluated using the electron binding energy of the 4s orbitals of both Pd centers as a proxy for oxidation state.<sup>12b,18</sup> During C–Cl reductive elimination from **5**, the binuclear core is reduced by two electrons. Delocalization, or sharing, of the additional electron density between two metal centers avoids reductive elimination intermediates in which any one metal center develops significant electronic charge. Consistent with the Pauling electroneutrality principle,<sup>1b,19</sup> the synergistic sharing of the electronic reorganization, which accompanies reductive elimination, between the two metals should lower the activation barrier to the redox process.

### Relevance of Binuclear Pd Complexes to Catalysis

Development of general, synthetically useful Pd-catalyzed C–H functionalization reactions requires discovery of both regioselective C–H palladation chemistry as well as development of reactions to efficiently oxidize the resultant organopalladium intermediates. General, regioselective C–H metallation remains a sought after challenge in synthetic chemistry.<sup>3</sup> Subsequent oxidation of the resultant organopalladium intermediates formed by C–H metallation, must be accomplished, and might proceed via a variety of mechanisms depending on the structure of the C–H metallation products. Determination of the nuclearity of the organopalladium intermediates relevant to catalysis by the tools of reaction kinetics requires knowledge of the nuclearity of the catalyst resting state as well as a reaction in which the turnover-limiting step does not precede redox chemistry.

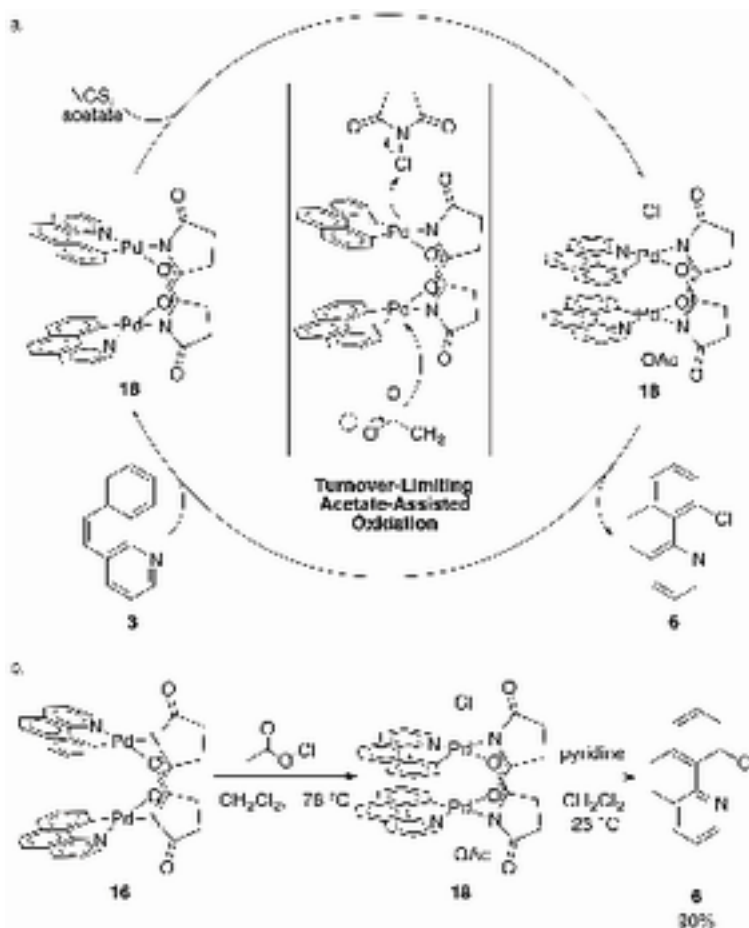
We have utilized Pd(OAc)<sub>2</sub>-catalyzed chlorination of benzo[*h*]quinoline (**3**)<sup>20</sup> to investigate the mechanism of oxidation during catalysis (Scheme 7a).<sup>21</sup> The catalyst resting state was determined to be succinate-bridged binuclear Pd<sup>II</sup> complex **16**, in which the Pd centers are held in proximity by the bridging succinate ligands (Pd–Pd = 2.8628(4) Å). In the presence of coordinating ligands, such as excess substrate as is present during catalysis, binuclear Pd<sup>II</sup> complexes can be in equilibrium with mononuclear Pd complexes;<sup>22</sup> however, binuclear resting state **16** is the only Pd complex observed under the conditions of catalysis (Scheme 7b).

**Scheme 7.** a. Pd(OAc)<sub>2</sub>-catalyzed chlorination of benzo[*h*]quinoline (**3**). Binuclear oxidation intermediates have been implicated during catalysis. b. Binuclear resting state **16** is entropically favored relative to mononuclear palladium complex **17** and is the only Pd complex observed during catalysis.



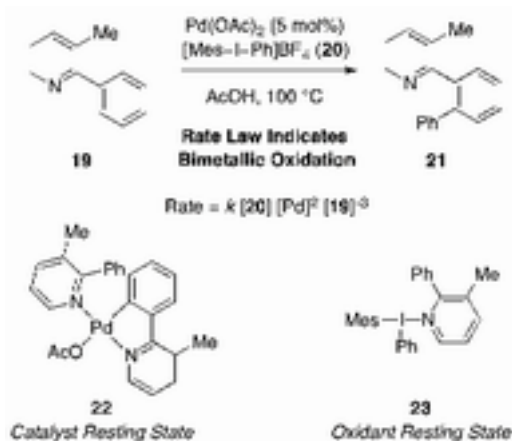
The rate law for  $\text{Pd}(\text{OAc})_2$ -catalyzed chlorination of **3** was determined to be  $\text{rate} = k[\mathbf{16}][\text{NCS}][\text{AcO}^-]$ . The determined rate law is consistent with acetate-assisted, bimetallic oxidation of **16** in the turnover-limiting step. Oxidation could proceed via pre-equilibrium association of acetate to **16** followed by oxidation with NCS, or reversible oxidation of **16** with NCS followed by acetate association. First order dependence on binuclear resting state **16** precludes the participation of mononuclear  $\text{Pd}^{\text{IV}}$  complexes in the rate-determining oxidation (Scheme 8a). Complex **18**, the proposed product of oxidation during catalysis, was independently prepared by oxidation of resting state **16** with acetyl hypochlorite, and was shown to be a chemically and kinetically competent intermediate for catalysis (Scheme 8b). The combination of both in situ monitoring of the kinetic profile of turnover-limiting oxidation as well as knowledge of the structure of the catalyst resting state has allowed unambiguous assignment of binuclear Pd intermediates in catalysis.

**Scheme 8.** a. Catalysis cycle for chlorination. Binuclear Pd intermediates have been implicated in oxidation during catalysis. Oxidation could proceed via pre-equilibrium association of acetate to **16** followed by oxidation with NCS, or reversible oxidation of **16** with NCS followed by acetate association. b. Proposed intermediate **18** has been prepared and shown to be chemically and kinetically competent for catalysis.



In 2009, Deprez and Sanford reported an investigation of oxidative Pd-catalyzed C–H arylation of 3-methyl-2-phenylpyridine (**19**) and found that oxidation is the turnover-limiting step in catalysis (Scheme 9).<sup>23</sup> Binuclear oxidation intermediates were implicated during catalysis based on a combination of catalyst resting state structure and in situ reaction kinetics measurements. Their study represents the only example, other than the chlorination discussed above, for which kinetic data relevant to oxidation during oxidative C–H functionalization catalysis with Pd is currently available.

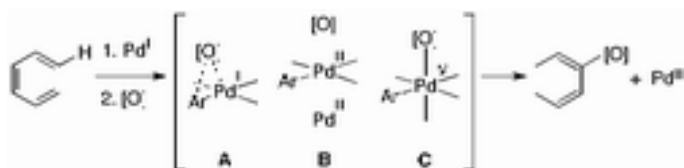
**Scheme 9.** Pd-catalyzed arylation of 3-methyl-2-phenylpyridine (**19**) proceeds with turnover-limiting oxidation. Based on the rate law of oxidation and the structures of the catalyst and oxidation resting states, kinetics measurements implicate binuclear oxidation intermediates.



## Proposal of $\text{Pd}^{\text{IV}}$ Intermediates

Oxidation of  $\text{Pd}^{\text{II}}$  intermediates, formed by C–H metallation during catalysis, could proceed by various mechanisms, including direct electrophilic substitution of the Pd–C bond (**A**, redox neutral at Pd),<sup>24</sup> oxidative addition to afford a binuclear  $\text{Pd}^{\text{III}}$  complex followed by reductive elimination (**B**), and oxidative addition to afford a mononuclear  $\text{Pd}^{\text{IV}}$  complex followed by reductive elimination (**C**) (Scheme 10). Reductive elimination from intermediate **B** can be bimetallic while reductive elimination from **C** is necessarily monometallic.

**Scheme 10.** Oxidative functionalization of the C–H bond could proceed via direct electrophilic substitution (**A**, redox neutral at Pd), oxidative addition to afford a binuclear  $\text{Pd}^{\text{III}}$  complex followed by reductive elimination (**B**), or oxidative addition to afford a mononuclear  $\text{Pd}^{\text{IV}}$  complex followed by reductive elimination (**C**). Reductive elimination from **B** can be bimetallic while reductive elimination from **C** must be monometallic.



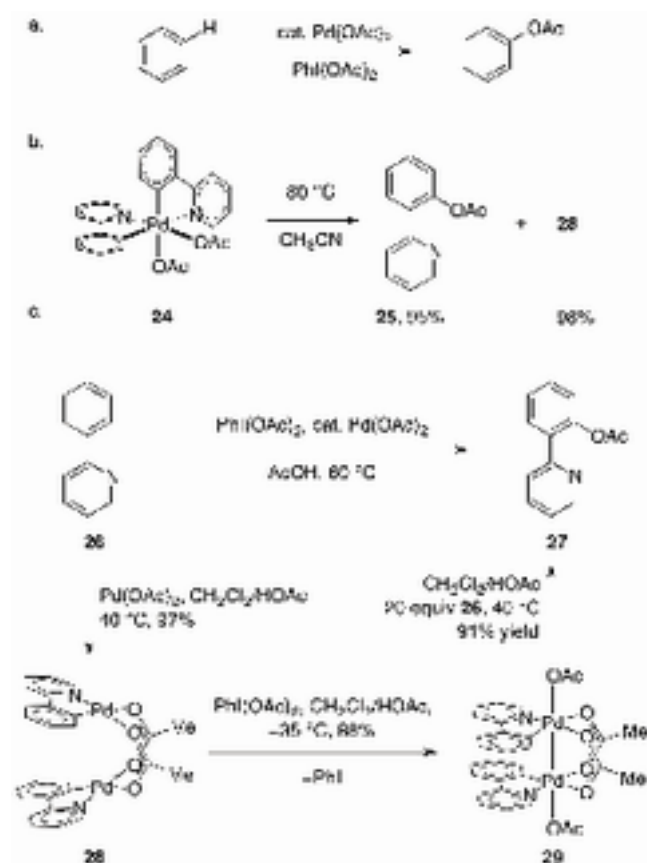
We believe that historically, mechanisms invoking the intermediacy of mononuclear Pd<sup>IV</sup> complexes have been favored and that the relevance of binuclear Pd<sup>III</sup> intermediates in catalysis has not been appreciated for two reasons: First, the reductive elimination chemistry of stoichiometric mononuclear Pd<sup>IV</sup> complexes is well established. Since a seminal report by Canty in 1986 documented that mononuclear Pd<sup>IV</sup> complexes can undergo C–C bond-forming reactions,<sup>25</sup> reductive elimination of C–O,<sup>26</sup> C–N,<sup>27</sup> C–Cl,<sup>27,28</sup> and C–F bonds<sup>29</sup> from mononuclear Pd<sup>IV</sup> centers have been reported. Second, C–H metallation, not oxidation, is typically the turnover-limiting step during catalysis.<sup>23</sup> For reactions in which metallation is turnover limiting, measurements of reaction kinetics obtained during catalysis provide information regarding the metallation step. Data relevant to the redox cycle in catalysis is frequently not available because metallation is turnover limiting.<sup>30</sup>

Investigation of the mechanism of Pd-catalyzed aromatic C–H acetoxylation illustrates the difficulty of using model systems to gain insight regarding intermediates in catalysis. Pd-mediated C–H acetoxylation was first reported in 1966.<sup>31</sup> Subsequent efforts have resulted in increasingly practical and valuable methods for the direct conversion of C–H to C–O bonds.<sup>20,32</sup> Since 1971, mononuclear Pd<sup>IV</sup> intermediates have been suggested in Pd-catalyzed C–H acetoxylation.<sup>20,33</sup> In 1996, Crabtree proposed mononuclear Pd<sup>IV</sup> intermediates in the acetoxylation of benzene using PhI(OAc)<sub>2</sub> as oxidant (Scheme 11a).<sup>34</sup> In 2005, Sanford suggested that Pd(OAc)<sub>2</sub>-catalyzed C–H acetoxylation proceeded via mononuclear Pd<sup>IV</sup> complexes and suggested diaryl mononuclear Pd<sup>IV</sup> complex **24** as a functional model of the putative Pd<sup>IV</sup> intermediates (Scheme 11b).<sup>26</sup> In 2009, we proposed that Pd(OAc)<sub>2</sub>-catalyzed acetoxylation may proceed through binuclear Pd<sup>III</sup> intermediates and demonstrated a synthesis cycle based on binuclear Pd<sup>II</sup> and binuclear Pd<sup>III</sup> complexes for the synthesis of C–OAc bonds (Scheme 11c).<sup>35</sup> We suggested that binuclear Pd<sup>III</sup> complex **29** may be the high-valent intermediate responsible for C–OAc bond formation during catalysis and we demonstrated that **29** is kinetically competent as a catalyst. Unlike studies of chlorination and arylation, the redox cycle relevant to acetoxylation catalysis has not been experimentally probed and as such, no information regarding the nuclearity of high-valent



intermediates in catalysis is currently available.

**Scheme 11.** a. Pd-catalyzed arene acetoxylation reactions have been proposed to proceed through  $\text{Pd}^{\text{IV}}$  intermediates. b. Mononuclear diaryl  $\text{Pd}^{\text{IV}}$  complexes have been shown to undergo C–O reductive elimination and have been proposed as models of high-valent intermediates in catalysis. c. Binuclear  $\text{Pd}^{\text{III}}$  complexes have been shown to undergo C–O reductive elimination and have been proposed as models of high-valent intermediates in catalysis.



While studies of model complexes such as **24** and **29** have shed light on the fundamental organometallic chemistry of mononuclear  $\text{Pd}^{\text{IV}}$  and binuclear  $\text{Pd}^{\text{III}}$  complexes, respectively, these studies were not carried out under conditions under which catalysis proceeds and thus provide no information regarding the redox cycle relevant to catalysis. Under conditions in which Pd-catalyzed acetoxylation of **26** is reported to proceed, C–H metallation is the turnover-limiting step ( $\text{KIE} = 4.3\text{--}5.1$ ).<sup>35,36</sup>

Measurements of reaction kinetics can only provide information about the redox cycle relevant to catalysis when the turnover-limiting step does not precede redox chemistry. Model complexes such as **24**, which has been shown to be kinetically incompetent as an intermediate in catalysis, can be excluded as catalysis intermediates, but no evidence in favor of models such as **29**, which is kinetically competent for catalysis, can be obtained.

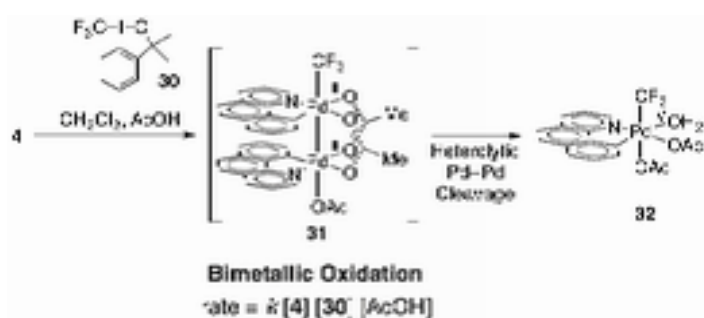
### Relevance of Mixed Valence Pd<sup>II</sup>Pd<sup>IV</sup> Intermediates

Stoichiometric oxidation of **4** with PhICl<sub>2</sub>, Br<sub>2</sub>, acetyl hypochlorite, and XeF<sub>2</sub> (vide infra) results in the formation of binuclear Pd<sup>III</sup> complexes. In 2010, oxidation of **4** with Togni's "CF<sub>3</sub><sup>+</sup>" reagent **30**<sup>37</sup> was reported to afford mononuclear Pd<sup>IV</sup> complex **32** (Scheme 12).<sup>38</sup> Given the similarity of the reported oxidation conditions to conditions we have previously reported to afford binuclear Pd<sup>III</sup> complexes, we speculated that **32** may be formed by fragmentation of an initially formed binuclear Pd<sup>III</sup> complex (i.e. **31**).<sup>15</sup> In principle, formation of **32** could arise by initial fragmentation of **4** to two mononuclear Pd<sup>II</sup> complexes followed by oxidation of a mononuclear Pd<sup>II</sup> complex directly to the observed mononuclear Pd<sup>IV</sup> complex (**32**), or by direct oxidation of **4** to a binuclear Pd<sup>III</sup> complex (i.e. **31**) followed by heterolytic Pd–Pd cleavage to afford a mononuclear Pd<sup>IV</sup> complex (**32**) and a Pd<sup>II</sup> complex. In 2010, Canty and Yates predicted that binuclear Pd<sup>III</sup> complexes bearing apical ligands with significantly different trans influences should resemble mixed valence Pd<sup>II</sup>Pd<sup>IV</sup> structures.<sup>39</sup> We viewed the observation of **32** upon oxidation of **4** as a potential venue for testing Canty's hypothesis regarding the valence asymmetry of binuclear complexes.

Analysis of the kinetic profile of the oxidation of **4** to **32** revealed the rate law to be rate =  $k$  [**4**][**30**][AcOH].<sup>15</sup> The observed rate law is analogous to the rate law observed for the Pd-catalyzed chlorination with NCS (Scheme 8) and suggests that binuclear complex **31** is the immediate product of oxidation of **4** with **30**. Subsequent fragmentation of **31**, which resembles the structures computed by Canty to be appropriately formulated as Pd<sup>II</sup>Pd<sup>IV</sup> mixed valence complexes, to generate mononuclear Pd<sup>IV</sup> complex **32**, confirms that the identity of the apical ligand has a dramatic effect on the electronic

structure of binuclear  $\text{Pd}^{\text{III}}$  complexes. While cleavage of Pt–Pt bonds in binuclear  $\text{Pt}^{\text{III}}$  complexes with differentiated apical ligands has been observed,<sup>40</sup> the formation of **32** from **31** represents the first example of M–M bond cleavage in binuclear  $\text{Pd}^{\text{III}}$  complexes. We propose that a similar heterolytic Pd–Pd cleavage may also be operative in the binuclear  $\text{Pd}^{\text{III}}$  intermediates bearing apical aryl ligands, which Sanford proposed as intermediates in C–H arylation (Scheme 9). While disproportionation of binuclear  $\text{Pd}^{\text{III}}$  complexes to mononuclear  $\text{Pd}^{\text{IV}}$  and  $\text{Pd}^{\text{II}}$ , as in the disproportionative cleavage to generate **32**, is apparently operative, at this point, the nuclearity and oxidation state of the complexes responsible for subsequent C–X bond formations are unknown. As we saw in our discussion of C–H acetoxylation (Scheme 11), the observation or isolation of high valent Pd complexes, regardless of their oxidation state or nuclearity, is not evidence of their relevance to C–X bond-forming reactions, and the presence of structures such as **31** and **32** during C–X bond-forming reactions does not establish their relevance in C–X bond formation

**Scheme 12.** Oxidation of binuclear  $\text{Pd}^{\text{II}}$  complex **4** affords mononuclear  $\text{Pd}^{\text{IV}}$  complex **32**. The rate law of formation of **32** is consistent with an initial bimetallic oxidation of **4**. Subsequent heterolytic Pd–Pd cleavage in putative oxidation intermediate **31** could afford **32**.

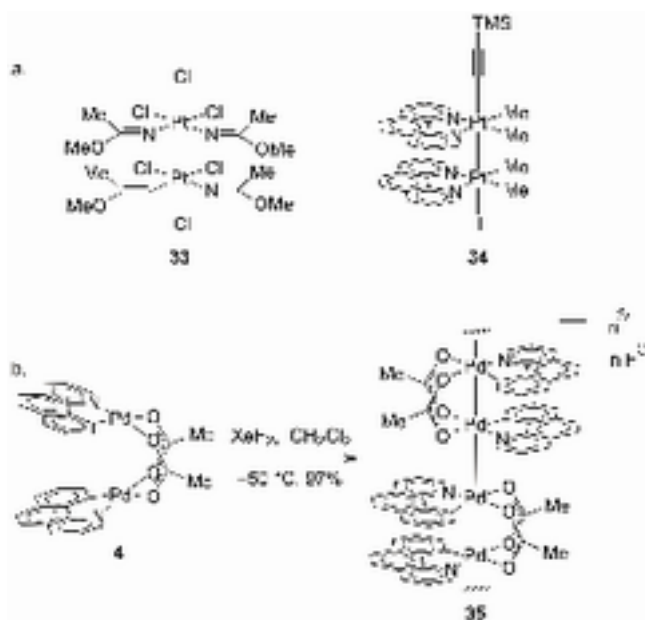


## Outlook

Currently, two reactions have been studied in which oxidation is turnover limiting during catalysis. Binuclear complexes have been implicated in oxidation in both reactions.<sup>21,23</sup> Given the prevalence of

reactions in which  $\text{Pd}(\text{OAc})_2$  is employed as catalyst and the propensity of acetate ligands to bridge two Pd centers, there are potentially many more reactions in which binuclear Pd complexes are involved in catalysis. A yet unresolved question is: Are bridging ligands required for the participation of binuclear intermediates in oxidation during catalysis? An evaluation of related organometallic chemistry suggests that the answer may be no: Binuclear  $\text{Pt}^{\text{III}}$  complexes **33** and **34**, with unsupported Pt–Pt bonds, have been prepared by oxidation of mononuclear  $\text{Pt}^{\text{II}}$  complexes (Scheme 13a).<sup>40</sup> Relatedly, we have found that oxidation of binuclear  $\text{Pd}^{\text{II}}$  complex **4** with  $\text{XeF}_2$  results in the formation of long chains of binuclear  $\text{Pd}^{\text{III}}$  complexes (**35**), which are supported by unbridged Pd–Pd bonds (Scheme 13b).<sup>41</sup> While there is not yet experimental evidence for unbridged binuclear intermediates in catalysis, if bimetallic oxidation, with M–M bond formation concurrent with oxidation, has a lower barrier than monometallic oxidation, binuclear intermediates may be present even in the absence of bridging ligands to pre-organize binuclear complexes. The generality and limitations of binuclear redox cycles in oxidation catalysis remain to be rigorously studied experimentally.

**Scheme 13.** a. Unbridged Pt–Pt bonds, formed by oxidation of mononuclear  $\text{Pt}^{\text{II}}$  complexes, have been crystallographically characterized. b. Oxidation of **4** with  $\text{XeF}_2$  affords long chains of Pd dimers (**35**) with unbridged Pd–Pd bonds.

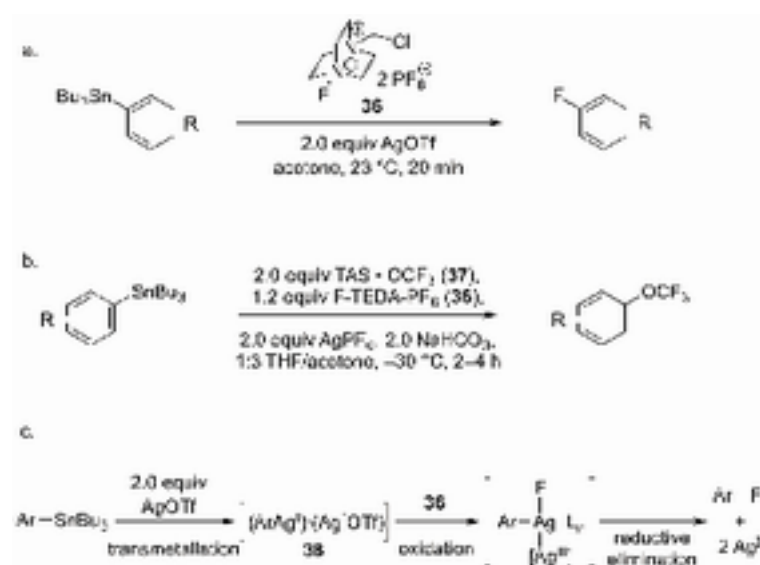


If bimetallic redox chemistry, in which two metals cooperatively participate in redox chemistry, can lower the redox barriers in Pd-catalysis, might similar effects be facilitating other known reactions? Binuclear rhodium catalysts, arguably one of the most synthetically useful class of binuclear transition metal catalysts developed by chemists, have been speculated to accomplish group transfer catalysis with bimetallic redox chemistry.<sup>42</sup> In the case of bimetallic Pd redox chemistry, while Pd-catalyzed C–H functionalization reactions have been developed over the past 40 years, the participation of high-valent binuclear intermediates was only recognized in 2009. Binuclear intermediates in Pd-catalyzed C–H functionalization reactions were not rationally targeted, and realization of potential M–M redox synergy has occurred subsequent to the discovery of many oxidative Pd-catalyzed transformations. In order to develop a conceptual framework that might enable rational design of bimetallic redox reactions for catalysis, an appreciation of the generality of bimetallic redox chemistry in catalysis is needed.

Our group has recently developed Ag-mediated fluorination and trifluoromethoxylation reactions of metallated arenes and has discovered a Ag-catalyzed fluorination reaction of aryl stannanes (Scheme 14).<sup>43</sup> While rigorous investigation of the mechanism of these transformations has not yet been carried out, we propose that polynuclear intermediates are involved and that bimetallic redox chemistry may

facilitate both the oxidation and subsequent C–X bond-forming steps. It has been found that two equivalents of  $\text{Ag}^{\text{I}}$  are required for high yields of fluorination.<sup>43a</sup> Aryl  $\text{Ag}^{\text{I}}$  complexes are known to form polynuclear aggregates,<sup>44</sup> and, given the expectation that  $\text{Ag}^{\text{III}}$  is an oxidation state too high to access under the employed reaction conditions, we have hypothesized that a bimetallic  $\text{Ag}^{\text{I/II}}$  redox cycle may be operative. Given the dearth of known Ag-catalyzed redox reactions, we believe that redox catalysis with Ag offers the opportunity to discover new redox transformations, which may rely on the cooperation of multiple metal centers.

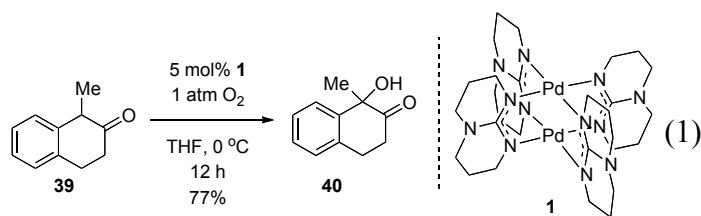
**Scheme 14.** a. Ag-mediated fluorination of aryl stannanes. b. Ag-mediated trifluoromethoxylation of aryl stannanes. c. Proposed mechanism for Ag-mediated fluorination of aryl stannanes. Polynuclear Ag-trifluoromethoxy intermediates are proposed intermediates in Ag-catalyzed trifluoromethoxylation of aryl stannanes.



We anticipate that future research will reveal the involvement of significantly more polynuclear complexes in redox catalysis in an increasing number of reactions, and believe that Pd, Ag, and Cu chemistry, as well as catalysis with first row transition metals, will be likely places for these discoveries to be made.

## Conclusion

High-valent Pd catalysis has been presumed to proceed through mononuclear Pd<sup>IV</sup> intermediates for much of the past 40 years. During this time, Pd-catalyzed C–H functionalization has emerged as a viable approach for the synthesis of many different C–heteroatom bonds, many of which are difficult to form with other transition metal catalysts. It is reasonable to ask whether elucidation of bimetallic redox chemistry has been a fruitful line of research, given the successful reaction development in its absence, or if it is only an academic curiosity. The realization of the possibility to lower redox barriers in catalysis by bimetallic redox chemistry can lead to the development of reactions that may not have been realized by targeting mononuclear oxidation intermediates. Based on the hypothesis that bimetallic redox chemistry with Pd can provide access to redox chemistry that is difficult to achieve with mononuclear catalysts, we investigated binuclear Pd complex **1** as a catalyst for Pd-catalyzed C–H oxidation with O<sub>2</sub>.<sup>45</sup> It was found that catalyst **1** is a dioxygenase-like catalyst for the alpha-hydroxylation of carbonyl compounds (Eqn. 1). The role of the binuclear core of **1** and the mechanism of oxygen activation are currently outstanding questions.



We anticipate that future research efforts will further shed light on binuclear intermediates in catalysis, both with Pd and other metals, and also that other pathways, such as direct electrophilic substitution of Pd<sup>II</sup>–C bonds and reductive elimination from mononuclear Pd<sup>IV</sup> complexes involved in catalysis may be discovered. It remains to be seen how new insight regarding the relevance of binuclear intermediates to catalysis will enable progress in reaction development.

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